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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	**PAPER NUMBER**
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	NOTIFICATION DATE	DELIVERY MODE
3 MONTHS	01/09/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Notice of this Office communication was sent electronically on the above-indicated "Notification Date" and has a shortened statutory period for reply of 3 MONTHS from 01/09/2007.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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TH

Office Action Summary	**Application No.** 10/677,853	**Applicant(s)** MATSUBARA ET AL.	
	Examiner Jeanine A. Goldberg	**Art Unit** 1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8* is/are pending in the application.

4a) Of the above claim(s) *5 and 6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the papers filed October 25, 2006. Currently, claims 1-8 are pending. Claims 5-6 have been withdrawn as drawn to non-elected subject matter.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow.

3. Any objections and rejections not reiterated below are hereby withdrawn.

A) Berlin (US 6,936,419) teaches an oligomer array with DNA oligomers on a surface which is for detecting cytosine methylation, however Berlin does not teaches a plurality of CpG dinucleotides on a single capture probe.

Maintained Rejections

Election/Restrictions

4. Applicant's election of Group I, Claims 1-4, 7 in the paper filed December 27, 2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The requirement is still deemed proper and is therefore made FINAL.

Priority

5. This application claims priority to Japanese document 2002-292122, filed October 4, 2002.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-4, 7-8 are rejected under 35 U.S.C. 102(b) as being anticipated by Fodor et al. (US Application 2001/0053519, December 20, 2001).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Fodor teaches oligonucleotide arrays comprising every 10-mer (less than 100-mer)(limitations of Claim 3, 7). Fodor teaches the regions containing individual probes, may be very small, usually less than about 100um x 100um, more usually less than about 50um x50um (para 123)(limitations of Claim 2). Fodor teaches many attachments of nucleotides to solid support mechanisms including the direct attachment of polynucleotides to cellulose by a method involving specific activation of the terminal

monosubstituted phosphate or polyphosphate of the polynucleotide by water soluble carbodiimide (para 78)(limitations of Claim 4).

A 10-mer array would inherently comprises an oligonucleotide sequence complementary to or identical to a nucleotide sequence in which all of C' other than C's in all CpG dinucleotides are replaced with T's and an oligonucleotide sequence complementary to or identical to a nucleotide sequence corresponding to a target sequence in which all of C's are replaced with T's.

Response to Arguments

The response traverses the rejection. The response asserts the claim has been amended to require that the oligonucleotide-immobilized substrate of the present invention "comprises capture probes, said capture probes consisting of multiple pairs of oligonucleotides wherein the capture oligonucleotide pairs consist of....". The response asserts that this limitation narrows the claims to a specific subset of capture oligonucleotides that are not taught by Fodor. This argument has been reviewed but is not convincing because the immobilized substrate comprises the capture probes with the recited properties. This indicates that the capture probes are immobilized on the substrate in addition to other probes. The claim is not limited to only these capture probe pairs. Thus, the additional probes of Fodor are encompassed by the instant claims. Since the array of Fodor is a complete 10-mer array every possible 10-mer is on the array and every possible pair is on the array. The array of Fodor therefore inherently encompasses

CGXXXCGXXX and TGXXXTGXXX
CGXCGXCGXX and TGXTGXTGXX, for example.

The claims no longer appear to read on capture probes that comprise additional CG dinucleotides which are replaced. For example, the claims no longer appear to be directed to CGXCGXTGXX or TGXTGXCGXX, for example. All of the C's are replaced with Ts or all of the C's are methylated.

Thus for the reasons above and those already of record, the rejection is maintained.

7. Claims 1, 3, 8 are rejected under 35 U.S.C. 102(e) as being anticipated by Garner et al. (US Publication 2003/0152950 A1, August 14, 2003).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Garner teaches identification of chemically modified polymers.

As seen in Figure 7, a 190bp region of the p16 promoter region is detailed and each of the CG regions are numbered for analysis (para 22). Garner teaches one set of features was a standard re-sequencing tiling for the sequence expected without methylation (i.e. all Cs converted to T). The other set was a standard re-sequencing tiling for the sequence expected with methylation of every C in each CpG step. The set of probes used in the array appear in Table 1 (para 57).

Garner teaches probe design by analysis of the sequence file. A probe list is created from the complementary sequence and every base is queried. One method for analysis, the first probe starts at position X and extended a number of bases, N. The next probe starts at position X+1 and extends N bases also (para 60). Where multiple CpG islands are on one probe, every possible combination of methylation sites from the parent probe must be created (para 61). For the promoter region of p16, the region contains 36 cytosines, as seen in Figure 7. Each of these cytosines is depicted in Table 2 where 16 cytosines are within CpG dinucleotides and 20 cytosines are not within CpG dinucleotides (para 84). The array was generated using 21 base probes (limitations of Claim 3, 7). Each 21-nucleotide probe is complementary to the sequence surrounding cytosine number 1, with a different base for each probe in apposition to cytosine number 1. As seen in Table 2, each cytosine was queried. Cytosines not part of a CpG were used as an internal standard for unmethyalted position (para 89).

Response to Arguments

The response traverses the rejection. The response asserts Garner teaches that additional position query probe partners may be required if multiple CpG islands are on one probe. Garner teaches "in this case every possible combination of methylation sites from the parent probe must be created (para 61). Furthermore, Garner teaches one set of features was a standard re-sequencing tiling for the sequence expected without methylation (i.e. all Cs converted to T). The other set was a standard re-sequencing tiling for the sequence expected with methylation of every C in each CpG step. The set of probes used in the array appear in Table 1 (para 57). Garner thus specifically contemplates multiple CpG islands on one probe (para 61) and all possible combination of probes. Therefore, since the instant claims are drawn to an immobilized substrate comprising capture probes, the substrate may comprise additional probes which are not limited to the recited capture probe pair qualities.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2, 4, 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Garner et al. (US Publication 2003/0152950 A1, August 14, 2003) in view of Fodor et al. (US Application 2001/0053519, December 20, 2001).

A recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim.

Garner teaches identification of chemically modified polymers.
As seen in Figure 7, a 190bp region of the p16 promoter region is detailed and each of the CG regions are numbered for analysis (para 22). Garner teaches one set of features was a standard re-sequencing tiling for the sequence expected without methylation (i.e. all Cs converted to T). The other set was a standard re-sequencing tiling for the sequence expected with methylation of every C in each CpG step. The set of probes used in the array appear in Table 1 (para 57).

Garner teaches probe design by analysis of the sequence file. A probe list is created from the complementary sequence and every base is queried. One method for analysis, the first probe starts at position X and extended a number of bases, N. The next probe starts at position X+1 and extends N bases also (para 60). Where multiple

CpG islands are on one probe, every possible combination of methylation sites from the parent probe must be created (para 61). For the promoter region of p16, the region contains 36 cytosines, as seen in Figure 7. Each of these cytosines is depicted in Table 2 where 16 cytosines are within CpG dinucleotides and 20 cytosines are not within CpG dinucleotides (para 84). The array was generated using 21 base probes (limitations of Claim 3, 7). Each 21-nucleotide probe is complementary to the sequence surrounding cytosine number 1, with a different base for each probe in apposition to cytosine number 1. As seen in Table 2, each cytosine was queried. Cytosines not part of a CpG were used as an internal standard for unmethyalted position (para 89).

Garner does not specifically teach dot size or means for immobilization.

However, Fodor teaches oligonucleotide arrays. Fodor teaches the regions containing individual probes may be very small, usually less than about 100um x 100um, more usually less than about 50um x50um (para 123)(limitations of Claim 2). Fodor teaches many attachments of nucleotides to solid support mechanisms including the direct attachment of polynucleotides to cellulose by a method involving specific activation of the terminal monosubstituted phosphate or polyphosphate of the polynucleotide by a water soluble carbodiimide (para 78)(limitations of Claim 4).

Therefore, the ordinary artisan would have been motivated to have used very small regions for placing the probe regions of Garner for the expected results of Fodor. Fodor specifically teaches the very small feature sizes allows very large numbers of probes to be located in very small regions for high throughput screening. The ordinary artisan would have been motivated to have used very small regions for immobilization of probes to facilitate the high density arrays.

Moreover, the ordinary artisan would have been motivated to have immobilize the capture oligonucleotides of Garner via carbodiimide groups taught by Fodor. Fodor teaches numerous binding immobilization methods including via carbodiimide groups which allows the specific immobilization.

Response to Arguments

The response traverses the rejection. The response asserts that Garner teaches that each CpG must be considered separately and that every possible change at a particular position must be queried. The response therefore suggests that additional query probe partners are required if multiple CpG islands are on one probe. However, as discussed above, Garner specifically teaches that multiple CpG islands may be present on one probe. Further, Garner teaches one set of features was a standard re-sequencing tiling for the sequence expected without methylation (i.e. all Cs converted to T). The other set was a standard re-sequencing tiling for the sequence expected with methylation of every C in each CpG step. The set of probes used in the array appear in Table 1 (para 57).

With respect to Fodor not directed to detection of methylation, Fodor is specifically directed to microarrays and their design. Designing arrays according to Fodor would have been obvious at the time the invention was made.

Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

10. No claims allowable over the art.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

A) Pao et al. (Human Molecular Genetics, Vol. 10, No. 9, pages 903-910) teaches the EDNRB promoter displays heterogeneous site specific methylation patterns in normal and tumor cells. Pao analyzed 11 individual CpG sites located throughout the CpG island. The data on the 11 individual CpG sites spanning the whole island demonstrated that several non-adjacent CpG sites showed high methylation in tumor tissues and some of the normal samples (page 904, col. 1). Pao teaches that increased methylation is found at CpG-130 the 5' most CpG dinucleotide analyzed which is located on the fringe of the CpG island (page 905, col. 1). Pao teaches CpG 336 remained resistant to hypermethylation even when adjacent CpGs were highly methylated. Some sites within the CpG island appeared to be preferential targets for de novo methylation whereas others seemed to be protected from hypermethylation changes (page 906, col.1).

B) Cameron et al. (Blood, vol. 94, No. 7, pages 2445-2451, October 1999) teaches the p15 CpG island methylation is heterogeneous. An analysis of the p15 CpG island illustrates that there was marked heterogeneity for the specific CpG sites methylated (abstract). Cameron teaches that the density of methylation within the CpG island and not any specific location correlates between with transcriptional loss (abstract). Cameron teaches that the importance of hypermethylation at 1 or 2 CpG sites and their location relative to transcription start sites remain to be determined (page 2445, col. 1).

C) Fajkusova et al. (Blood Cells, Molecules and Diseases, Vol. 26, No. 3, June 2000) teaches a detailed mapping of methylcytosine positions at the CpG island surround the Pa promoter in the bcr-abl locus. Table 2 illustrates the homogeneity across the island.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (571) 272-0743. The examiner can normally be reached Monday-Friday from 7:00 a.m. to 4:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

The Central Fax Number for official correspondence is (571) 273-8300.

J. Goldberg
Jeanine Goldberg
Primary Examiner
January 3, 2007